Chromosome 1p terminal deletion: report of new findings and confirmation of two characteristic phenotypes

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Abstract

We report three unrelated patients with small terminal deletions involving 1p36.22→pter that occurred de novo and compare our patients to the 10 previously reported cases. Although our patients have an identical cytogenetic deletion, patients 1 and 2 share similar clinical features that differ substantially from patient 3. Our patients confirm the existence of two characteristic phenotypes in 1p36.22→pter deletion. Both phenotypes share some dysmorphic features, but are differentiated by characteristics of growth failure versus macrosomia. In addition, we report the new finding of cardiomyopathy and hydrocephalus in the phenotype associated with growth failure. It is possible that different phenotypic subgroups may exist because of differences in the parental origins of the deleted chromosome or of variations in undetectable amounts of genetic material.

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A review of the published reports shows that terminal deletions of the short arm of chromosome 1 are rare.[1] We report three unrelated patients with a deletion of 1p36.22→pter.

Case reports

PATIENT 1

Patient 1 was delivered at 41 weeks by caesarean section for failure to progress, weight 2600 g (<10th–50th centile for 36 weeks), length 43·3 cm (<10th–50th centile for 13 weeks). She presented at the age of 3 weeks with congestive heart failure. Cardiac evaluation showed a patent foramen ovale, patent ductus arteriosus (PDA), and left ventricular dysfunction (table 1) that was more severe than could be explained by her relatively minor structural defects. Metabolic aetiologies of cardiomyopathy were excluded (table 1). Thyroid function was also normal. The PDA was ligated at 1 month of age, after failing a trial of indomethacin.

Further evaluation showed hydrocephalus, OFC 35 cm (10th centile), and dysmorphic features including a small face with midline hypoplasia, frontal bossing, large anterior fontanelle, small, upward slanting palpebral fissures, low set ears with right preauricular ear pits, microstomia, and polydactyly of the left hand (fig 1). Chromosome analysis showed a subtle deletion of the terminal portion of the chromosome 1 short (p) arm. Her karyotype was 46,XX,del(1)(p36.22) (fig 2). Parental karyotypes were normal.

At 2 years of age, the cardiomyopathy has resolved and her hydrocephalus is stable without shunt surgery. She has esotropia, and has developed mild right sided hemihypertrophy with normal abdominal ultrasound. Developmentally, she has been moderately delayed. On examination, weight was 10·3 kg (<5th–50th centile for 15 months), height 82·8 cm (<5th–50th centile for 14 months), and head circumference 47 cm (10th centile). The dysmorphic facial features had remained the same. The right thigh measured 25 cm, left $24\frac{1}{2}$ cm, right lower calf $17\frac{1}{2}$ cm, and left 17 cm.

PATIENT 2

Patient 2 was delivered at 35 weeks by caesarean section for oligohydramnios and intrauterine growth retardation, weight 1749 g (10th centile). She had a complicated neonatal course with apnoea, bradycardia, and grade II IVH. She was noted to have dysmorphic features (fig 3) including a large anterior fontanelle, small palpebral fissures, bilateral iris colobomas, low set, small ears, and microstomia. Chromosome analysis showed a terminal deletion of chromosome 1p with a 46, XX,del(1)(p36.22) karyotype (fig 2). Parental karyotypes were normal.

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Table 1 Cardiovascular and laboratory findings

	Age	*Structural defects*	*Shortening fraction*	*Ejection fraction*	*Evaluation*
Patient 1	1 mth	PDA/dilated LV	25%	68%	Normal: organic acids, acylgylcines, acylcarnitines, carnitine level, thyroid function (T4, TSH)
	1 y	None	Normal	Normal	
Patient 2	2 mth	None	17%	39%	
	9 mth	None	Normal	Normal	
Patient 3	12 mth	None	Normal	Normal	Normal: very long chain fatty acids, biotinidase, urine oligosaccharides, and musopolysaccharides, thyroid function (T4, TSH).

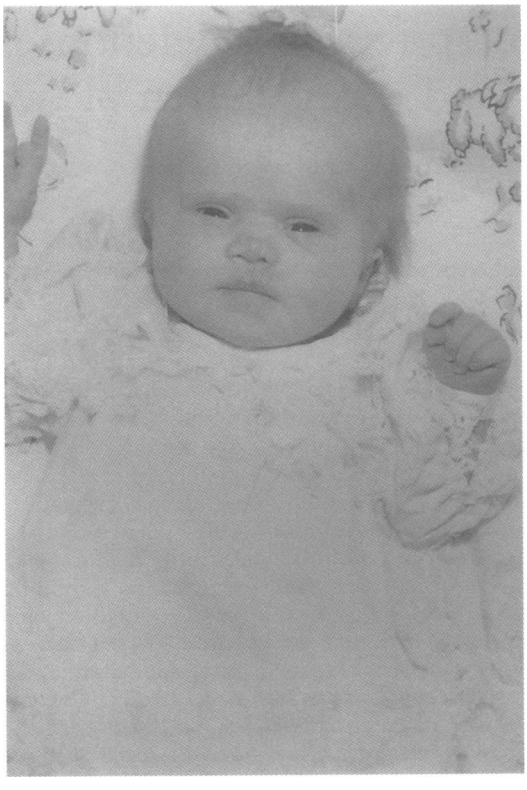

Figure 1 Patient 1 at 1 month.

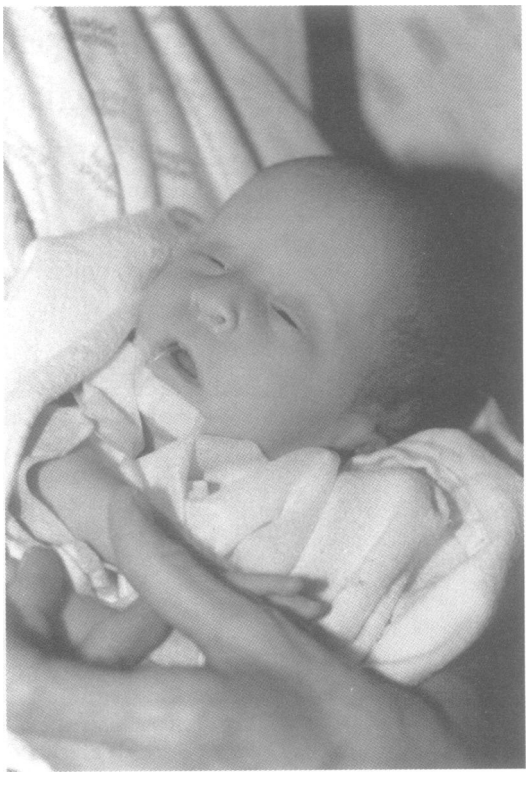

Figure 3 Patient 2 at $1\frac{1}{2}$ months.

On hospital admission at 6 weeks of age for continued apnoea/bradycardia with cyanosis, this patient was noted to have marked hypotonia. Cranial ultrasound showed hydrocephalus. Echocardiography showed a structurally normal heart but significant left ventricular dysfunction (table 1). At 3 months, her weight was 4 kg (10th centile), height 52 cm (<5th centile), OFC 37·5 cm (25th centile).

By the age of 9 months, the cardiomyopathy had resolved. At 18 months, her hydrocephalus has remained stable and has not required shunting, and her head circumference has remained at the 10th–25th centile. Her development has

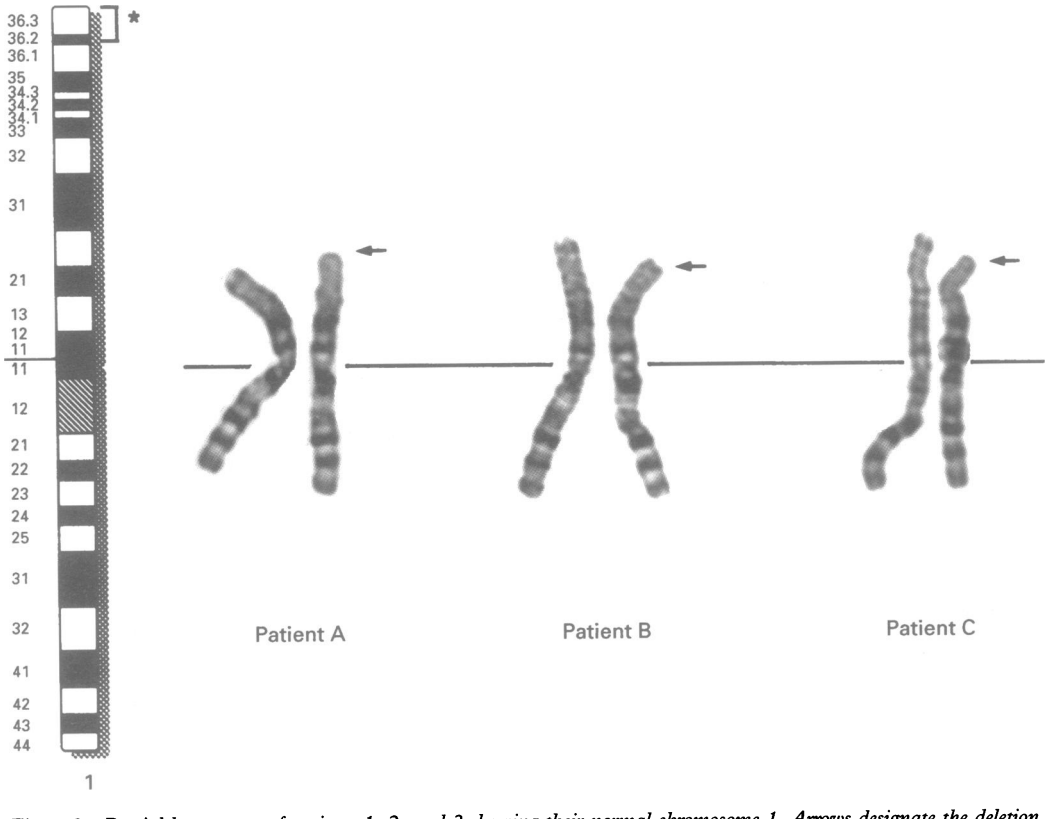

Figure 2 Partial karyotypes of patients 1, 2, and 3 showing their normal chromosome 1. Arrows designate the deletion (1) (p36.22) of their other chromosome 1. Each karyotype was at a 550 or greater band level.

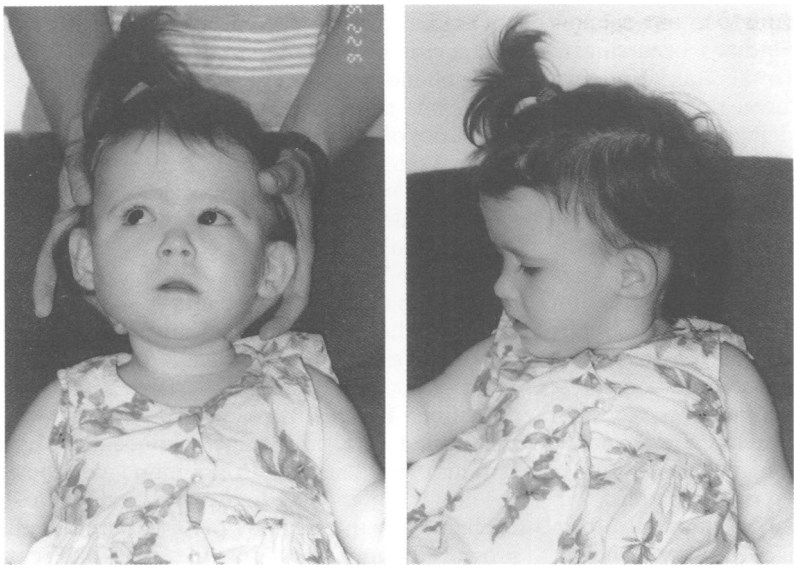

Figure 4 Patient 3 at 17 months.

been profoundly delayed with a developmental quotient of 30. Her height has increased to <5th centile (50th centile for $12\frac{1}{2}$ months) with weight <5th centile (50th centile for 8 months).

PATIENT 3

Patient 3 was born at 39 weeks by caesarean section secondary to breech presentation, weight was 2720 g (30th centile), length 49·5 cm (60th centile), OFC 35 cm (90th centile). The mother was 25 years old, G4 P1 Ab3, whose pregnancy was complicated by multiple flu-like illnesses. The infant's newborn period was complicated by seizures, gastro-oesophageal reflux, poor feeding, and aspiration pneumonia. The gastro-oesophageal reflux was treated with the medication Reglan.

She was seen in consultation at 12 months of age for severe developmental delay and myoclonic seizures. On examination, her growth parameters showed weight 11 kg (90th–95th centile), height 84 cm (>95th centile), and OFC 46 cm (60th centile). Dysmorphic features included hypotonia, large anterior fontanelle, brachycephaly, hypertelorism, inferior epicanthic folds, low set ears with prominent auricular roots, flat nasal bridge, tapered fingers with fifth finger clinodactyly, and a telangiectatic skin lesion on her mid forehead with several hyperpigmented macules on her extremities (fig 4). Metabolic studies were normal, including blood for very long chain fatty acids and biotinidase, and urine for oligosaccharides and mucopolysaccharides, and thyroid function (table 1). Echocardiogram was normal (table 1). Chromosome analysis showed a 46,XX,del(1)(p36.22) karyotype (fig 2). Parental karyotypes were normal. At 20 months of age, her development remains severely delayed with functioning at a 3 to 4 month level. Growth parameters include weight 11·8 kg (75th centile), height 85 cm (75th centile), and head circumference 45·5 cm (5th centile).

Table 2 Selected clinical features in reported cases of chromosome 1p terminal deletions

Features	*Patients*			*Previous Reports*	*Total (%)*
	1	*2*	*3*		
Microcephaly	−	−	−	7/8	7/11 (64)
Large fontanelle	+	+	+	1/2	4/5 (80)
Small palpebral fissures	+	+	−	6/8	8/11 (73)
Cleft lip/palate	−	−	−	2/3	2/5 (40)
Depressed nasal bridge	+	−	+	7/9	9/12 (75)
Low set ears	+	+	+	7/9	10/12 (83)
Cardiac defects	+	−	−	3/5	4/8 (50)
Cardiomyopathy	+	+	−	0/2	2/5 (40)
Hydrocephalus	+	+	−	1/3	3/6 (50)
Growth failure	+	+	−	3/4	5/7 (70)
Macrosomia	−	−	+	0/4	1/7 (14)
Mental retardation	+	+	+	9/9	12/12 (100)
Hypotonia	+	+	+	3/3	6/6 (100)
Seizures	+	+	+	2/4	5/7 (70)

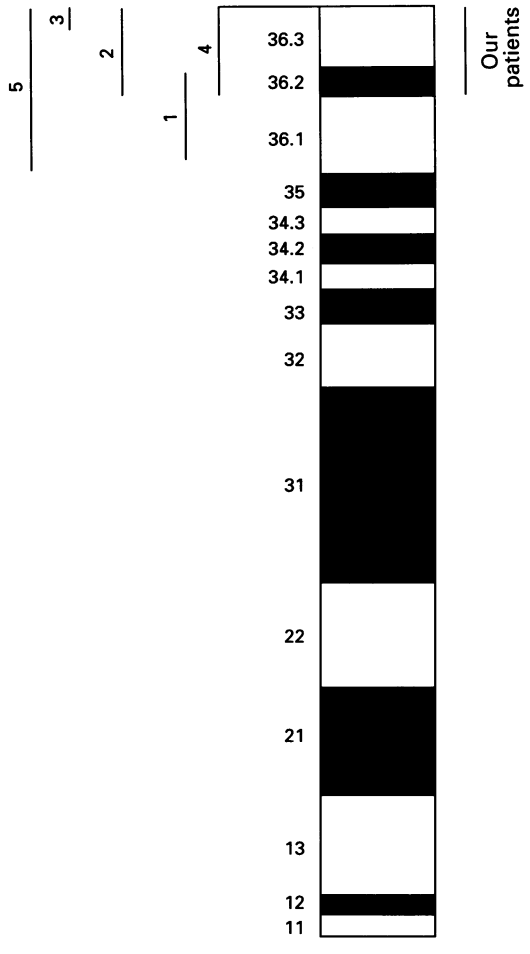

Figure 5 Breakpoints on the short arm of chromosme 1 in 13 reported cases with numbers representing the listed references.

Discussion

Our patients bring to 13 the total reported cases of patients with very small terminal deletions involving chromosome 1p36.22, none of which involves translocation. Like our patients, the previous 10 had de novo deletions; one was an interstitial deletion and the remainder were terminal deletions. A diagram of the breakpoints on the short arm of chromosome 1 in the 13 reported cases is shown in fig 5.

Although these patients share some common manifestations, there does not appear to be one clearly defined phenotype for chromosome 1p36.22 deletion. Table 2 compares selected clinical features of our three patients with the 10 previously reported cases. A total of 22

clinical features were identified in our patients and reported patients. Findings occurring in 30% or more included mental retardation, low set ears, hypotonia, seizures, depressed nasal bridge, short neck, clinodactyly, upward slanting palpebral fissures, cryptorchidism, growth failure, cardiac defects, microcephaly, large fontanelle, flat occiput, and small eyes. The cardiac defects described in previous patients included a small ventricular septal defect,[1] tetralogy of Fallot,[2] and infundibular stenosis of the right ventricle.[5] There were no patients reported with associated cardiac dysfunction.

Our patients had many common features, including large anterior fontanelles, low set ears, hypotonia, and developmental delay. However, although our patients had a similar chromosome deletion, growth patterns in patients 1 and 2 differed substantially from patient 3. Patient 3 had macrosomia with height at the 95th centile at birth, and height and weight at the 75th centile at 20 months. In contrast, patients 1 and 2 had growth failure with height and weight <5th centile.

In addition, we describe the previously unreported findings of cardiomyopathy and hydrocephalus in two patients with growth failure. Although patient 1 had a PDA, the cardiomyopathy persisted long after repair of the PDA. Patient 2 had no structural lesion that would explain the cardiomyopathy. Neither patients 1 or 2 had any significant cardiovascular structural abnormality or metabolic abnormality that could account for their cardiomyopathy. Patient 2 had only a grade II IVH, and although this might explain the hydrocephalus in this patient, in patient 1 there was no recognised aetiology for the hydrocephalus. In both patients, the cardiomyopathy resolved and the hydrocephalus has not required shunting.

Our patients confirm the existence of two characteristic phenotypes of del(1)(p36.22). Both phenotypes share some dysmorphic features, but are differentiated by growth characteristics of growth failure versus macrosomia. Wargowski *et al*[6] also described two distinguishable but overlapping phenotypes: those with impairment of growth and those with obesity and physical characteristics similar to the Prader-Willi syndrome. His four patients had terminal deletions of band 1p36 (not specified further) with other features including postnatal short stature, severe psychomotor retardation, large anterior fontanelle, narrow palpebral fissures, broad, flat nasal root, malformed ears, fifth finger clinodactyly, hypotonia, and seizures. In addition, we report the new findings of cardiomyopathy and hydrocephalus in the phenotype associated with growth failure. It is possible that different phenotypic subgroups may exist because of differences in the parental origins of the deleted chromosome or submicroscopic differences in the amount of deleted genetic material.

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